A Generalized Microdosimetric Dose Response Model

Shirin Rahmanian[1], Tony C. Slaba[2], Floriane Poignant[1]

[1]Analytical Mechanics Associates, Hampton, VA; [2]NASA Langley Research Center, Hampton, VA

Background

- To ensure astronaut safety during and after deep space missions, it is imperative to accurately project radiation health risks.
- The current NASA cancer risk model relies on dose-rate modifiers and radiation quality factors (QF) to scale available epidemiological models based on acute gamma ray exposures to the low dose rates and complex mixed particle fields found in space.
- QF models describe the increased biological effectiveness of particles found in space compared to gamma exposures and represent the major source of uncertainty plaguing cancer risk projections [1].
- Underlying these QF models are experimental dose-response data obtained in cell cultures and animals that provide a basis for estimating relative biological effectiveness.
- As part of a broader effort to better understand and reduce QF uncertainties, dose-response models need to be improved and/or developed.

Objective

- In this work, a microdosimetric dose response model is applied to the harderian gland (HG) tumorigenesis experimental dataset [2].
- The model assumes that observed biological responses should be correlated with, if not predictable from, doses received by microscopic-scale targets [3] (see Figure 1).
- To the authors knowledge, this microdosimetric model has never been applied to the HG dataset.
- The performance of the microdosimetric model against the HG data set was evaluated and compared to a linear dose response model [2].

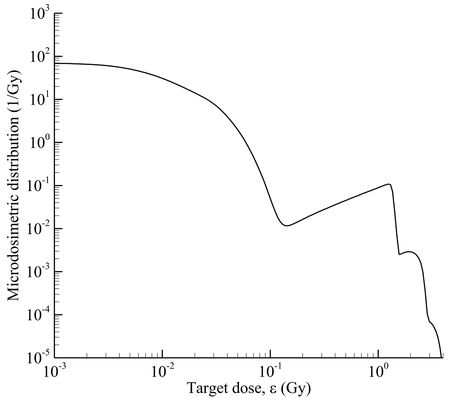

Figure 1. Distribution of doses received by spherical targets with radius 2.76 μm irradiated by 0.1 Gy of 600 MeV/n ^{56}Fe.

Modeling Methods

Microdosimetric Model

- The general form of the microdosimetric dose-response model is

$$P(\mathbf{B}) = \int \kappa(\varepsilon) f(\varepsilon;\mathbf{B})\, \varepsilon\, d\varepsilon \qquad (1)$$

- P denotes the observed biological response (e.g. HG tumorigenesis)
- $\mathbf{B}$ denotes the collection of beam and target parameters.
- $f(\varepsilon;\mathbf{B})$ is the calculable microdosimetric distribution for spherical targets. e.g. spherical target with radius 2.76 μm exposed to 0.1 Gy of 600 MeV/n ^{56}Fe, as in Figure 1.
- $\kappa(\varepsilon)$ is an unknown kernel function relating microscopic target doses to observed biological responses.

Biophysical Expansion

- The microdosimetric distribution, f, can be separated into biophysically meaningful components (see Figure 2) according to

$$f(\varepsilon;\mathbf{B}) = f_0(\varepsilon;\mathbf{B}) + f_1(\varepsilon;\mathbf{B}) + f_n(\varepsilon;\mathbf{B}) \qquad (2)$$

- $f_0(\varepsilon;\mathbf{B})$ - (red) targets that were not directly traversed by an ion track,
- $f_1(\varepsilon;\mathbf{B})$ - (green) targets that were directly traversed once,
- $f_n(\varepsilon;\mathbf{B})$ - (blue) targets that were traversed more than once.
- Note that both f_1 and f_n include contributions from δ-rays of nearby tracks.
- Substitute equation (2) into equation (1), and make the approximation that the kernel function is constant for each of the microdosimetric components. The resulting model is given by

$$P(\mathbf{B}) = \kappa_0 d_0(\mathbf{B}) + \kappa_1 d_1(\mathbf{B}) + \kappa_n d_n(\mathbf{B}) \qquad (3)$$

$$d_i(\mathbf{B}) \equiv \int f_i(\varepsilon;\mathbf{B})\, \varepsilon\, d\varepsilon \qquad (i = 0,1,n) \qquad (4)$$

- where κ_0, κ_1, and κ_n are free parameters quantifying the tumorigenic potential of the three target populations.
- We also test the simplified 2-parameter model

$$P(\mathbf{B}) = \kappa_{01}[d_0(\mathbf{B}) + d_1(\mathbf{B})] + \kappa_n d_n(\mathbf{B}) \qquad (5)$$

- where κ_{01} is a free parameter accounting for both d_0 and d_1 target populations.

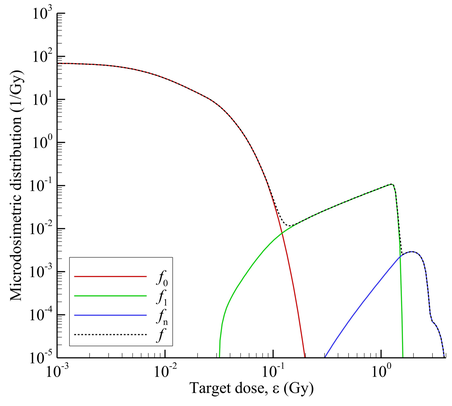

Figure 2. Same as Figure 1, but the microdosimetric distribution, f, has been separated into biophysically meaningful components.

Results

- A linear dose-response model from Chang et al. [2] is compared to the microdosimetric model in Figure 3 and Table 1.
- A high-dose attenuation term, $e^{-\alpha D}$, for cell killing/sterilization is applied as a multiplicative factor to all models tested. The saturation coefficient, α, is treated as an adjustable parameter.
- The microdosimetric distributions are computed using RITRACKS [4] and convolution integrals [5].
- The microscopic target radius is also treated as an adjustable parameter (i.e. not fixed to 2.76 μm).
- Parameters are calibrated to available HG tumorigenesis experimental data for heavy ions [2].

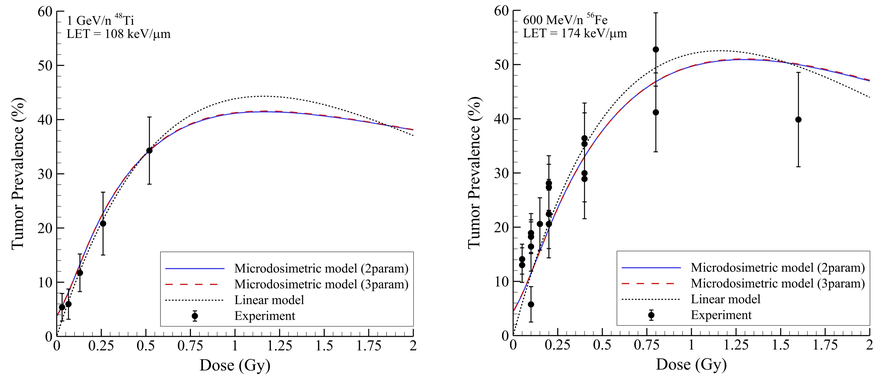

Figure 3. Comparison of models to experimental data for 1 GeV/n Ti (left) and 600 MeV/n Fe (right).

Table 1. Summary of model performance against HG tumorigenesis experimental data set for heavy ions only.

	Optimal target radius (μm)	Total number of parameters	R^2	Akaike Information Criterion (AIC)
Microdosimetric model (2 parameter*)	2.69	4	0.864	259.5
Microdosimetric model (3 parameter*)	2.67	5	0.865	261.3
Linear model**	N/A	4	0.860	260.8

** Microdosimetric models include either 2 or 3 parameters along with the adjustable target radius and the saturation coefficient, α.*
*** The linear model [2] is given as $P = (a+bLe^{-cL})De^{-\alpha D}$, where a, b, c, and α are adjustable parameters, and L is the ion linear energy transfer (LET).*

Conclusions and Future Work

- In this work, a microdosimetric dose response model was presented.
- The model relates observed biological responses to microscopic-scale spherical target doses.
- The optimal target radius was found to be very close to the HG nuclear radius of 2.76 μm.
- The microdosimetric model has a higher R^2 and lower AIC compared to the linear model.
- The microdosimetric model predicts charge and energy dependence of dose-response through the biophysical spectra contained in equations (1) – (5).
- Ongoing and future work will include:
  - Consideration of strictly numerical integral expansions including basis splines.
  - Inclusion of empirical low-dose (non-targeted effects) corrections.
  - Application of model to chromosome aberration datasets for fibroblasts and lymphocytes.
  - Incorporate model into an ensemble framework with statistical weighting.

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